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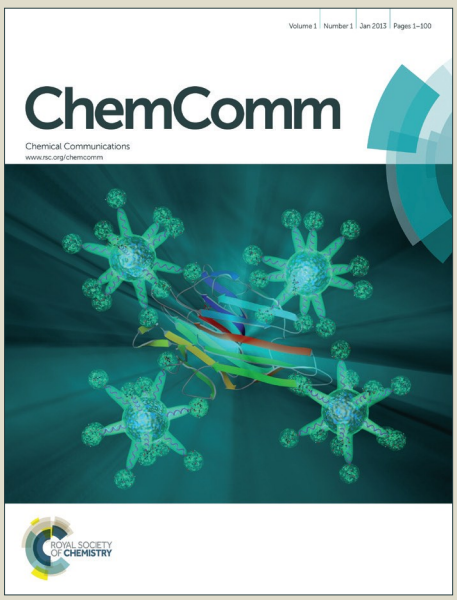

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Outstanding drug loading capacity by water stable microporous MOF: A potential drug carrier†

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A robust, highly water stable (up to 3 weeks), microporous MOF, $[Zn_8(O)_2(CDDB)_6(DMF)_4(H_2O)]$ {where CDDB = 4,4'-(9-H Carbazole-3,6-diyl)dibenzoic acid}, was solvothermally synthesized based on an open N─H site, exhibit outstanding loading capacity (around 53.3 wt %) and satisfactory release capability (64.9 % and 81.9 %) of 5-Fluorouracil consisting a negligible cytotoxicity effect.

It is a great challenge to synthesize new bioactive compounds with therapeutic activity and/or a low aqueous solubility. So the developing of the process becomes very slow for their commercialization. This problem may be overcome by suitable carriers having better loading and releasing capability, to improve the activity of known molecules. These carriers usually offer a better control of the drug plasmatic levels, increasing the efficiency by reducing toxicity, as well as an increase in the drug stability by protection of the biodegradation. In this regards polymeric and mixed systems have been proposed for a better drug release.[1] However, this process leads to a decrease of the drug storage capacity.[2]

Since last decades, compared to prior unsuccessful drug carrier systems, an alternative route (the hybrid route) has been proposed using porous metal-organic frameworks (MOFs). These materials offer several advantages as the structures are highly tuneable, which can be accomplished through a change of the metal and/or organic linker to effectively tune the pore size, structure and chemical properties.[3] These solids grab a high pore volume (fraction of void volume to total volume), a regular porosity, and the presence of active binding site within the framework which allows an ease adoption of guest molecules and offer unprecedented opportunities for their uses in the areas of biomedicine and medicine.[4] So, an encouraging efforts have therefore been devoted on these fields; *e.g.*, the delivery of bioactive gas molecules,[5] Gd^{3+} based nanoscale MOFs being used as magnetic resonance imaging (MRI) contrast agents,[6] and lanthanide based MOFs being efficient multimodal cellular probes materials.[7] Particularly, MOFs as drug-delivery carriers are highly desirable in view of their large loadings of drugs, biodegradability, and versatile functionality.[8,9]

MOFs as drug delivery systems was first confirmed by Férey and colleagues in 2006 that two MOFs – MIL-101 (Cr) and MIL-100 (Cr),[8] which exhibited remarkable capacity for drug loading and controlled delivery. However, due to the presence of toxic metal (Cr), the materials described in these reports were not compatible with biomedical applications. Subsequently, many researchers were devoted on this topic and several works has been done using different drug molecules.[9] Among them, the drug molecule, 5-Fluorouracil (5-FU) is very important as it is used for cancer treatment for anal, breast, colorectal, oesophageal, stomach, pancreatic and skin cancers (especially head and neck cancers)[10] and called as anticancer drug. It is used in chemotherapy,[11] but not extensively due to lack of its suitable carrier. To overcome this problem, Zhou and co-workers prepared porous MOF consisting nanocage, Cu(pi)-PEG5k.[12] Unfortunately the 5-FU loading capability was 4.38 (wt %), which is not good enough., Conversely, Wang and colleagues reported a MOF which could load 33.3 (wt %) 5-FU within the pores and release them slowly.[13] Several efforts, after this work, were observed with the same drug having lower loading property,[12–20] presented in tabular form (Table S1).

Considering the previous studies, we synthesized a robust bi-carboxylate ligand 4,4'-(9-H Carbazole-3,6-diyl)dibenzoic acid[21] (H_2CDDB, Supplementary Scheme 1). In our strategy, the zinc and H_2CDDB are selected based on the following considerations: (i) the zinc is non-toxic and biocompatible; (ii) H_2CDDB, as a V-shaped ligand, favours the generation of suitably porous architectures with high rigidity; (iii) the open N─H site may support to adsorb drug molecules with some interactions which may favour a large extent of drug loading capacity (hydrogen bonding or van der Walls interactions). Reaction of $Zn(NO_3)_2{\cdot}6H_2O$ and H_2CDDB in DMF under solvothermal condition yields a porous MOF $[Zn_8(O)_2(CDDB)_6(DMF)_4(H_2O)]$ (**1**) having suitable pore for 5-FU loading. At room temperature, pH = 7.4, **1** exhibits an outstanding drug loading capacity 53.3 wt%, greatly exceeding the previous record of 33.3 wt% at the same condition. Furthermore, this MOF is highly stable in water and shows stability up to 3 weeks. The non-toxic nature of **1** was confirmed by the MTT assay against the human hepatoblastoma cell line (HepG2) and human breast ductal carcinoma cell line (MDA-MB-435S) after 12 h incubation with MOF, suggesting the safety of MOF.

Single crystal X-ray diffraction experiments‡ revealed that the MOF crystallizes in monoclinic system space group $P2_1/a$, and the asymmetric unit includes eight Zn atoms, two O atoms, six CDDB, thirteen DMF and fourteen H_2O molecules and formulated as $[Zn_8(O)_2(CDDB)_6(DMF)_4(H_2O)](DMF)_9(H_2O)_{13}$, which is confirmed by elemental analysis and TGA (See Experimental section). The

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crystal structure adopts two types of SBU, where the core of each SBU consists of a single O atom bonded to four Zn atoms, forming a regular Zn_4O tetrahedron (Figure 1), somewhat similar to MOF-5.[22] In the first SBU, one edge of Zn tetrahedra is in octahedral geometry, capped by three $-CO_2$ groups, two DMF and the central O atom, whereas remaining three are in tetrahedral geometry, one of which is coordinated by two $-CO_2$ groups, one H_2O and the central O atom and other two are capped by three $-CO_2$ groups and the central O atom (Figure 1a-c), resulting to form a $Zn_4(CO_2)_6(O)$ cluster (two DMF and H_2O are omitted). In the second SBU, one edge of Zn is coordinated by $-CO_2$ group instead of one H_2O and other three edges are same with first one (Figure 1d-f), forming a $Zn'_4(CO_2)_6(O)$ cluster (two DMF are omitted, Zn′ denotes second SBU). Each type of SBU is surrounded by three other SBU forming a propeller type packing (Figure S1) and these three propeller together forms a large 2D hexagonal ring where two different SBU act as alternative vertex and the bridging ligands CDDB as edge of that. (Figure 1g). Based on these connections, Zn^{2+} and the ligand CDDB alternately generate a 2D undulating layer with large void that they allow another undulating layers to penetrate in a parallel manner, giving a 2D–2D double 2-fold interpenetrating network (Figure S2) and resulting a 1D channel through *a*-axis (Figure 1i). Interestingly, inspection along *b*-axis two successive interpenetrating layers exhibit helical packing through (101) plane (Figure 1h). The size of the channel is estimated from the distance between two Zn^{2+} ions to be 28.1 Å × 23.17 Å (Figure S2).

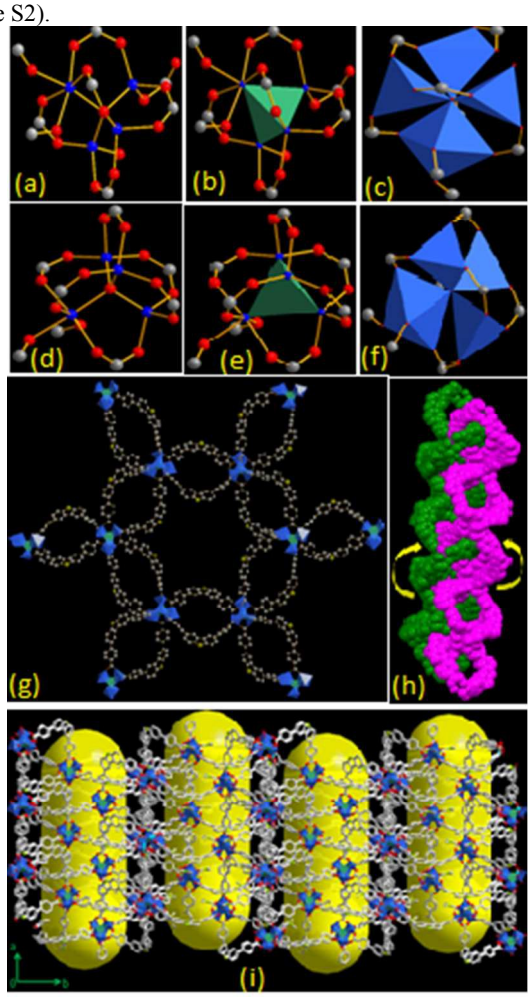

Figure 1. Construction of the **1** framework (a) The $Zn_4(O)(CO_2)_6(DMF)_2(O)$ and (d) the $Zn_4(O)(CO_2)_6(DMF)_2$ cluster as a ball and stick model (Zn, blue; O, red; C, grey). (b) And (e) the same with the $Zn_4(O)$ tetrahedron indicated in green. (c) And (f) the same but now with the ZnO_4 tetrahedra indicated in blue. (g) 2D hexagonal ring where two different SBU act as alternative vertex and the bridging ligands CDDB as edge. (h) Helical packing through (101) plane. (i) Side view of 1D channel through *a*-axis having sixe 28.1 Å × 23.17 Å, indicated by a yellow cylinder, formed by double interpenetrating 2-fold 2D network.

In order to better understand the underlying topology of the 2D network of 1, a 'node and linker' approach was undertaken. In this treatment, $Zn_4(CO_2)_6(O)$ clusters are 3-connected nodes (Fig. 1g), and the resulting network has (6, 3) topology (Figure S3). Furthermore, each 2D network, which is parallel to the (101) plane, is interlocked in a parallel fashion (along the *b* axis) with neighbouring ones to give access to a 3D framework, exhibiting the entangled feature of 2D + 2D to 3D polycatenation. (Figure 1i).[23] The PLATON[24] calculation indicate that **1** is microporous (see N_2 adsorption, Figure S4) and the total potential solvent volume is 9075.4 $Å^3$, which corresponds to 41.6% (21825.9 $Å^3$) empty volume. Overall, the framework structure is neutral by the consideration of charge balance, and DMF and H_2O molecules are residing in the channels, as determined by elemental analysis (EA), thermogravimetric analysis (TGA).[13] The TGA (Figure S5) data reveal a weight loss of 8 % from room temperature to 120 °C, which can be attributed to the loss of H_2O molecules. Thereafter, a small weight loss (27 % at 350 °C) prior to decomposition was observed, which corresponds to the loss of DMF molecules and solvent guest molecule.

The drug delivery capacity of **1** was evaluated by adsorption of anticancer drug 5-FU into it and experiment was carried out by impregnating desolvated **1** (See S3 at Supplementary) under stirring in 5-FU containing methanol solutions. **1** was desolvated under a dynamic vacuum ($<10^{-3}$ Torr) at 100 °C overnight prior to insertion of the drug. The 5-FU containing MOF maintains its crystalline property as evidenced by PXRD (Figure 2a). The incorporation of the drug molecule during adsorption process is confirmed by Fourier transformed infrared spectroscopy (FTIR) (Figure 2b) with presence of ν (C−H) at 2931 cm^{-1} and vibrational bands characteristic of the −O−C−O– groups between 1663 and 1342 cm^{-1}. And the absorption band at about 1239 cm^{-1} may be due to fluorine atom on the ring.[25] In addition, the shift of the ν (C=O) band of the carboxylic group of 5-FU from 1691 cm^{-1} to 1723 cm^{-1} correlated to those of the ν (N−H) vibrational band of **1** from 3747 to 3720 cm^{-1}, indicates the formation of a hydrogen bond between the carbonyl group of 5-FU and the amino group of **1**.(Figure 2b)

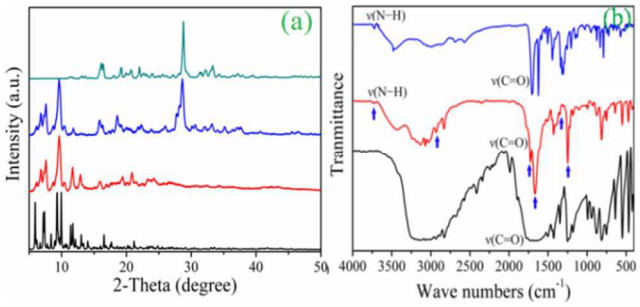

Figure 2. (a) PXRD patterns for 1 (simulated, black; desolvated 1, red; 5-FU-loaded 1, blue; 5-FU, dark cyan) (b) IR spectra of 5-FU, black; 1 loaded with 5-FU, red and activated 1, blue.

To determine the effective storage capacity of **1** UV–vis absorption spectroscopy has been used (Figure S6). To get a maximum drug loading, 5-FU to porous solid relative ratio was tested (Table S2). It was observed that adsorbed amount of 5-FU increased

with initial 5-FU/ material ratio expressed in weight and optimal value (5:4) corresponding to maximum solubility of 5-FU in methanol. In the previous study it was reported that the contact time is also an important factor for drug loading. But surprisingly the contact time does not affect the amount drug loading in this MOF. The maximum adsorption was same after 1 or 2 or 3 days, which may indicate a large tendency to encapsulate the drug molecules. Thus, the loading experiment were performed by soaking desolvated **1** for 1 day in a 5 mg mL^{-1} 5-FU containing methanol solution with a 5-FU to desolvated **1** weight ratio of 5:4. Chemical analysis and TGA result (Supplementary Figure S5) indicates that it encapsulates around 53.3 wt% of 5-FU in desolvated **1**, corresponding to 0.66 g of 5-FU, which is the highest amount in all the reported so far.[12–20] The quantitative comparisons between the structure and the uptake, PLATON[24] calculations were used. The calculated result shows that the theoretic uptake of 5-FU by desolvated **1** is about 0.62 g 5-FU. Therefore, it can be concluded that the total pore volume has been used for uptake of 5-FU molecules. The difference between the theoretic and experimental values indicates that 2–4% external surface sorption still exists, even after washing.

The sustained-release of anticancer drug experiments were performed by dialyzing the drug-loaded **1** against phosphate buffered saline (pH 7.4) and deionised water (pH 6.9) at 37 ºC and measured by fluorescence spectrophotometer.[13] A satisfactory release was observed without any "burst effect". The fluorescence spectra of 5-FU delivery at 37 ºC are shown in Figure S7. The delivery of 5-FU occurred within 3 days and 64.9% (in PBS) and 81.9% (in deionised water) of the loaded drug was released (Figure 3). The degradation of **1** was characterised by PXRD and TGA. The PXRD pattern confirmed that **1** retained its crystallinity to some extent after drug releasing (Figure S8). The size (morphology) of the particle of **1** was shown in Figure S9, where it observed that after drug release it becomes too small.

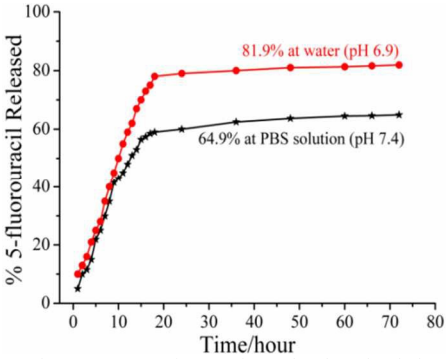

Figure 3. The release process of 5-FU from the drug-loaded **1** (% 5-FU vs. time).

As mentioned above, the crystal structure have 1D channel larger than the size of the drug molecule (5.3 Å × 5.0 Å) consisting open N─H site which is helpful to store large amount of drug molecule. Though from the structural view point in the channel two different environment may persist for the guests.[26] But surprisingly, instead of our expectation (two different regimes) the loaded drug released only in one step. A large amount of drug loading, may be the probable reason, which may facilitate large number of strong interactions among the drug molecules even those are far away from the walls. And the large number of drug-drug interactions may be equivalent to those hydrogen bonds and π–π interactions[8, 27] between 5-FU and the organic part of the skeleton, which may give result only one step drug release.

Beside the drug delivery study, we have performed the water stability of **1**. Because this is the most important supporting factor since **1** act as carrier. The water stability experiments were carried out in deionised water for 3 weeks, boiling water (100 ºC) for 1 day and in hot water (2 days at 85 ºC). But in hydrothermal (85 ºC) condition the framework is stable up to 12 hour, beyond that it goes to a different crystalline phase. The achievement of high water stability of this MOF may be due to double 2-fold interpenetration, which make the robust structure. Due to 2D packing there is no chance to collapse the framework. In this regards, this MOF is more practical than the famous MOF-5 as it is unstable is water even in dense humid condition.[28] The stability in different conditions are characterized by PXRD (Figure S10).

In order to evaluate its potential anticancer activity, we carried out the *in vitro* experiments with **1** and drug loaded **1.** The experimental details were given in Supplementary Information (S5. *In vitro* Cytotoxicity Test). The non-toxic nature of **1** was confirmed by the MTT assay against two cell lines including the human hepatoblastoma cell line (HepG2) and human breast ductal carcinoma cell line (MDA-MB-435S). Two different concentrations (100 μg mL^{-1} and 80 μg mL^{-1}) of **1** were used in the assay, which showed that 93.2% of viable HepG2 and 94.5 % of MDA-MB-435S cells were present at the maximum dosage of 100 μg mL^{-1} of **1** with respect to the control (Figure 4). On the other hand, 5-FU loaded **1** exhibited significant anticancer activity. 77.9% of viable HepG2 and 78.9 % of MDA-MB-435S cells were present at 80 μg mL^{-1} of 53.3wt% 5-FU loaded **1** treatment while only 78.6% of viable HepG2 and 69.6% of MDA-MB-435S cells were present with 100 μg mL^{-1} (Figure 4).

We observed no significant difference in the amount of viable HepG2 cells (78.6% and 77.9%) between the two groups treated with different dosage of drug loaded MOFs (100 μg mL^{-1} and 80 μg mL^{-1}, respectively), indicating the maximal efficacy of drug loaded MOFs on HepG2 cells. In contrast, Human breast cancer cells MDA-MB-435S exhibited a dose-dependent manner when treated with drug loaded MOFs. This result probably due to the property of anticancer drug 5-FU we applied in this study.[29]

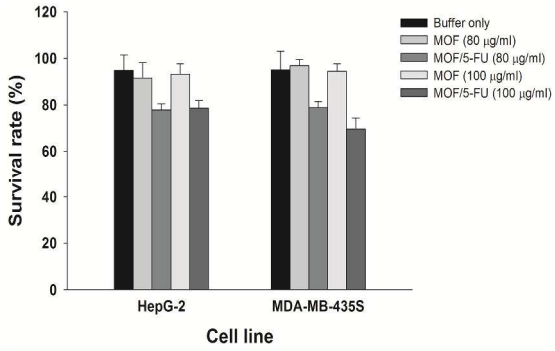

Figure 4. Cytotoxicity of **1** and 5-FU loaded **1** against HepG2 and MDA-MB-435S cell line.

In conclusion, a robust, highly water stable, microporous MOF, was solvothermally synthesized by employing the concept of an open N─H site, which is helpful to encapsulate large amount of drug molecule. Considering its big channel and open N─H site, **1** has been used as materials for the adsorption and delivery of anticancer drug 5-FU and the experimental results indicate that it shows high drug loading (53.3 %) and slow release of the proportion of the loaded drug with a delivery time of about three days. The non-toxic nature of **1** was confirmed by the MTT assay against the human hepatoblastoma cell line (HepG2) and human breast ductal carcinoma cell line (MDA-MB-435S) at both concentrations (80 μg/ml and 100 μg/ml) after 12 h incubation with MOF, suggesting the safety of MOF. The high water stability of **1** make it unique and more useful as a potential carrier for other bio active molecules or drugs. The size selective drug delivery study among few important drugs and improved releasing

property by **1** is in under progress. We are also currently undertaking the open N─H site functional CDDB ligand to other metal salts for the other biomedical applications. We believe this work will open a new avenue to overcome the carrier problem for bioactive molecule.

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Notes and references

‡ Crystallographic data of 1: $C_{168}H_{118}N_{10}O_{31}Zn_8$, M = 3295.85, monoclinic, space group $P2_1/a$, a = 15.4739(2), b = 57.1814(6), c = 24.7469(3) Å, β = 94.6020(10) deg, V = 21825.9(5) A^3, Z = 4, μ = 1.405 mm^{-1}, D_c = 1.002 g cm^{-3}, $F(000)$ = 6736, (R_{int} = 0.1302), R_1 = 0.1114, wR_2 = 0.2154 ($I > 2\sigma(I)$), GOF = 1.364. Max./min. residual electron density 2.148 and -1.565 e·A^{-3}. A total of 42631 data were measured in the range $3.26 < \theta < 73.43$. The data were corrected for absorption by the multiscan, giving minimum and maximum transmission factors of 0.940 and 0.983, respectively.

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26 Firstly, the drug molecules which are approaching to the walls, the forces are dominated by strong host–guest interactions from the hydrogen bonds (N─H···N or N─H···O or N─H···F) and π–π interactions between 5-FU and the organic part of the skeleton. Secondly, the drug molecules far away from the walls, the forces are mainly from comparatively weak intermolecular interactions than former, namely 5-FU–5-FU interactions.

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29 Meanwhile, we did not find the anticancer activity when we incubated the cell lines with either MOFs or drug loaded MOFs for short time, for example within 5 h (data not shown), indicating the slow release effect caused by the drug (5-FU)loaded MOFs. This is in line with the result we observed from the release process of 5-FU from the drug loaded MOFs (Figure 3).